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DOI: https://doi.org/10.1007/s12311-014-0633-9

Cerebellum (2015) 14:308–316
DOI 10.1007/s12311-014-0633-9

REVIEW

Cerebellar Cysts in Children: a Pattern Recognition Approach

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Published online: 15 December 2014

Abstract Cerebellar cysts may be seen in selected genetic disorders and acquired anomalies. Here, we review our experience, excluding cystic tumors and parasitic cysts. The pathogenesis is heterogeneous: Cysts may involve/represent normal structures (e.g., Virchow-Robin spaces), be "destructive" (such as in some types of pontocerebellar hypoplasias), "malformative" (such as in some forms of congenital muscular dystrophies and *GPR56*-related migration disorders), or "disruptive" (such as in some cerebellar dysplasias). The provided checklist may be useful in deciding targeted diagnostic workup.

Key words Cerebellar cysts · Cerebellar dysplasia · Pontocerebellar hypoplasia · Congenital muscular dystrophy

Introduction

Cerebellar cysts are rather uncommon findings in pediatric neuroimaging and may be seen in selected disorders of both malformative and disruptive etiology. The provision of checklists for cerebellar imaging anomalies prompted us to compile disorders which may go along with cerebellar cysts [1]. Here, we present an extensive and illustrated update and review our experience and the available literature. In this context, we do not consider cerebellar tumors with a cystic component (such as low-grade gliomas and hemangioblastomas), parasitic cysts (such as echinococcus cysticus and alveolaris and neurocysticercosis), or posttraumatic and postsurgical cysts, but we refer to corresponding textbooks and specific references [2–5]. In addition, we do not refer to posterior fossa cystic malformations such as Dandy-Walker malformation, posterior fossa arachnoid cysts, or Blake's pouch cysts. The pathogenesis of cerebellar cysts is heterogeneous. An overview is summarized in Table 1. For orientation, we are suggesting broad categories as "signposts" based on the underlying pathomechanism. This classification aims to allow an imaging pattern recognition approach and takes into account clinical information. We conclude the description of each category with hints for the typical neuroimaging constellation.

Generally, cerebellar cysts may have a different size and shape, a heterogeneous location within the cerebellum, a hypointense signal on T1-weighted and fluid attenuation inversion recovery (FLAIR) images, and a hyperintense signal on T2-weighted images; do not enhance after intravenous injection of gadolinium-based contrast agent; and do not show abnormal diffusion on diffusion-weighted imaging.

For clarification, we recapitulate the following definitions: A *malformation* is defined as a morphological defect of an organ, part of an organ, or a larger region of the body resulting from an intrinsically abnormal developmental process. A *disruption* is defined as a morphological defect of an organ, part of an organ, or a larger region of the body resulting from an extrinsic breakdown of, or an interference with, an originally normal developmental process [6, 7].

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Table 1 Differential diagnosis of cerebellar cysts in children

Subgroups		Etiology	Comments
Normal structure	Cystic PVS	MPS	Mostly types I + II, rare type III
Isolated cyst(s)		Neuroglial cyst(s)	
Destructive cyst		PCH	Types 1, 2, 6
Malformative		Aicardi syndrome	
		GPR56-related	
		CMD	Mostly α-dystroglycanopathy (e.g., *FKRP*, *POMT2*, *LARGE*, *POMGnT1*)
			Rarely *LAMA2*-related
		LAMA1-related	
Cerebellar dysplasia		Genetic	Cohen syndrome (rare)
		Unknown pathogenesis (genetic vs. acquired)	Diffuse, bilateral dysplasia + cysts
		Disruptive	Focal dysplasia + cysts
Miscellaneous	LCC		
	Early-onset multiple carboxylase deficiency		

CMD congenital muscular dystrophy, *LCC* leukoencephalopathy with calcifications and cysts, *MPS* mucopolysaccharidosis, *PCH* pontocerebellar hypoplasia, *PVS* perivascular space

Cysts Involving Normal Structures

Cystic Dilatation of Perivascular Spaces

Perivascular spaces (PVSs) or Virchow-Robin spaces may be found almost everywhere in the brain. Predilection sites are the lateral borders of the anterior commissure, the subcortical and deep white matter, the mesencephalon, and the cerebellum around the dentate nucleus. Focal dilatation of PVS has been reported in about 2 % of the population. Dilatation of PVS can be observed in healthy people or maybe associated with various diseases. On magnetic resonance imaging (MRI), PVSs have a sharp demarcation, a cerebrospinal fluid-like signal on all pulse sequences, demonstrate no enhancement, occur along the path of penetrating arteries, and, if dilated, may cause mass effect. The pathogenesis of enlarged PVS is still unclear, and no clinical significance is assumed [3].

In mucopolysaccharidoses (MPSs), particularly types I and II, PVSs are often enlarged in the following anatomical regions: periventricular and subcortical white matter, corpus callosum, basal ganglia, thalamus, and brainstem [8]. In addition, cystic dilatation of PVS may be seen in the hilus of the dentate nucleus and the surrounding cerebellar white matter [9]. Two main pathophysiological mechanisms have been proposed for the formation of enlarged PVS in MPS: (1) storage of glycosaminoglycans around the vessels and (2) impairment of reabsorption of cerebrospinal fluid caused by mucopolysaccharide deposition in the leptomeninges [9]. In addition, less common posterior fossa neuroimaging findings in MPS may include mega cisterna, hypoplasia of the cerebellar vermis, or macrocerebellum [9]. Figure 1 shows cystic dilatation of cerebellar PVS in a patient with MPS type 3 Sanfilippo. The presence of the cysts can serve as a key element in targeting diagnostic investigations. Recognition

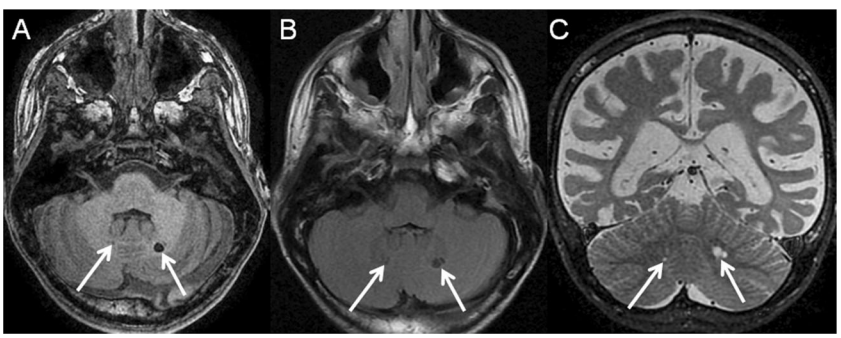

Fig. 1 A 10-year-old child assessed for developmental regression. A diagnosis of MPS III-A (Sanfilippo) was confirmed. Axial T1-weighted (**a**), axial fluid attenuation inversion recovery (FLAIR) (**b**), and coronal T2-weighted (**c**) images show enlarged perivascular spaces in the bilateral cerebellar white matter and adjacent dentate nuclei (*arrows*). Marked supratentorial atrophy is also noted (**c**)

of the underlying metabolic disorders is typically not problematic considering the overall clinical and imaging aspects.

Typical constellation: cystic PVS dilatations are located in the cerebellar white matter, in the region of the dentate nucleus, in an otherwise normal cerebellum.

Isolated Cysts

Neuroepithelial Cysts

Neuroepithelial cysts—also called neuroglial cysts or glioependymal cysts—are benign fluid-containing smooth, round, or ovoid cavities which may occur throughout the neuraxis; most are supratentorial. They do not contain calcifications or hemorrhage. They are isointense or slightly hyperintense to cerebrospinal fluid on T2-weighted imaging, suppress on FLAIR, and do not enhance. In addition, on FLAIR images, there is no surrounding hyperintense gliotic tissue. Neuroepithelial cysts are usually unilocular and mostly incidental and asymptomatic findings [3]. Rarely, they are space-occupying in the posterior fossa [10]. Marsh et al. reported a patient with Joubert syndrome and evolving neuroepithelial cysts in the brain, mesencephalon, and cerebellum [11]. In our personal neuroimaging cohort of more than 130 patients with Joubert syndrome, we have never encountered cerebellar cysts [12].

Typical constellation: mostly single cyst in the white matter, usually an incidental finding, in a normal cerebellum.

Destructive Cerebellar Cysts

Pontocerebellar Hypoplasias

Pontocerebellar hypoplasias (PCHs) are a heterogeneous (clinical, imaging, and genetic) group of disorders [13]. At present (August 2014), Online Mendelian Inheritance in Man (OMIM) lists ten types. While type 3 and type 8 are considered "developmental" (i.e., not progressive), the other types are progressive diseases. The concept of these prenatal onset degenerative conditions was put forward by Peter Barth who defined the type 1 and type 2 in the early 1990s [14].

Cerebellar cysts of destructive origin were primarily reported in detail in postmortem specimens in PCH2. Cyst formation in the cerebellar white matter was found in 2/7 patients [15]. The border of the cysts was lined by reactive astrocytes and macrophages. Large cysts were seen on MRI in one patient at the age of 1 month, located at the lateral aspects of the hemispheres [15]. A further patient was illustrated in a subsequent larger cohort [16]. The overall prevalence of cysts in PCH1 and PCH2 is rather low. In a series of 14 children with PCH1 and associated *EXOSC3* mutations, cerebellar cysts have been found only in three patients [17]. All children had p.D132A heterozygous/compound mutations. The cysts were located in the lateral aspects of the cerebellar hemispheres.

Cerebellar cysts have been also described in a single child with PCH6, a much less prevalent form [18]. Other articles on patients with PCH6, however, did not report on cerebellar cysts [19, 20].

Typical constellation: few cysts in the lateral aspects of the cerebellar hemispheres in a severely abnormal cerebellum, dominated by atrophy (hemispheres more than vermis), and pontine hypoplasia.

Malformative Cysts

Aicardi Syndrome

Aicardi syndrome (MIM 304050) is a rare disorder characterized by the "classical" triad of infantile spasms, corpus callosum dysgenesis, and chorioretinal lacunae. Additional common features are microphthalmia, cataracts, microcephaly, growth retardation, precocious puberty, and vertebral as well as rib anomalies. Aicardi syndrome is considered to occur as de novo dominant X-linked with lethality in the hemizygous male, observed only in females, and exceptionally in XXY individuals.

Neuroimaging extends beyond callosal dysgenesis and usually includes a wide spectrum of additional anomalies like interhemispheric and intraventricular cysts, extensive areas of polymicrogyria, subependymal and cortical heterotopias, tectal dysplasia and posterior fossa anomalies, and abnormal white matter myelination (Fig. 2). Cerebellar abnormalities are overall frequent including inferior vermis hypoplasia, dysplastic or hypoplastic hemispheres, and subcortical and periventricular heterotopias [21]. In the series reported by Hopkins et al., cysts were present in 4/23 girls [21].

Typical constellation: characteristic clinical setting in a female infant with ophthalmological abnormalities and infantile spasms and a combination of supratentorial (in particular, agenesis of corpus callosum and polymicrogyria) and infratentorial imaging abnormalities. Cerebellar cysts are present in about 20 % of the patients.

Cerebellar Cysts Associated with *GPR56* Mutations

GPR56 mutations were identified in patients with extensive (supratentorial) migration disorders (polymicrogyria) [22]. These authors identified 14 patients and 1 fetal case. Of 13 MRI available for analysis, frontoparietal polymicrogyria was

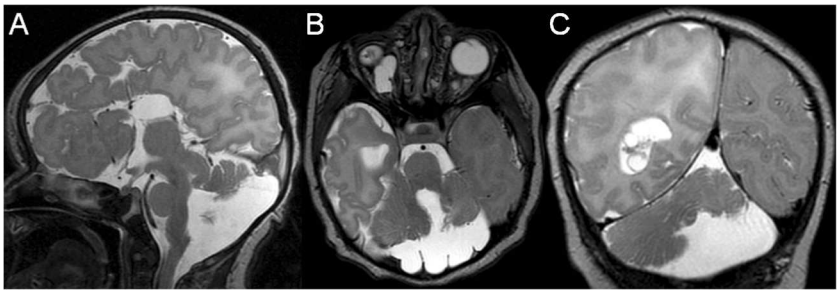

Fig. 2 A 2-month-old infant with Aicardi syndrome. Midsagittal T2-weighted image (**a**) shows agenesis of the corpus callosum, tectal dysplasia, and cerebellar hypoplasia. Axial T2-weighted image (**b**) reveals right microphthalmia and cerebellar hypoplasia and dysplasia. Coronal T2-weighted image (**c**) shows cerebellar hypoplasia and dysplasia, supratentorial migration abnormality, and right intraventricular cysts

found in 4/13 and generalized polymicrogyria with an anterior to posterior gradient in 9/13. All patients had patchy to diffuse myelination abnormalities. Cerebellar dysplasia was a feature in all individuals. Cerebellar cysts were present in 11/13 MRI and had a subpial and cortical location. The brain stem was inconsistently hypoplastic. The clinical picture was dominated by severe motor and cognitive impairment. Generalized seizures occurred in 12/14 patients. This supratentorial and infratentorial imaging pattern was confirmed by Barkovich [23]. Quattrocchi et al. reported on five *GPR56* mutated children, and cerebellar cysts were a consistent feature [24]. A single child was described by Fuji et al. [25]. Multiple cysts were illustrated in the corpus callosum, but not in the cerebellum. In addition, no cerebellar cysts are mentioned in the single case reported by Luo et al. [26].

Animal experiments in mice provide compelling evidence that *GPR56* plays a key role in regulating pial basement membrane during cortical development. Loss of mouse Gpr56 leads to neuronal ectopia, neuronal overmigration, and a cobblestone-like malformation [27]. Although this study was focused on development of cerebral cortex, it is likely that comparable effects on pial basement membrane in the cerebellum are involved in development of cerebellar dysplasia and cysts. A pediatric patient with *GPR56* mutation is illustrated in Fig. 3.

Typical constellation: multiple cysts associated with cerebellar dysplasia and abnormalities of the supratentorial white matter and cortical architecture, in a patient with seizures and intellectual disability.

Congenital Muscular Dystrophy Spectrum

The great progresses of neuroimaging in the last decades showed that cerebellar cysts as well as signal changes of the supratentorial white matter, migrational abnormalities, and abnormal cerebellar foliation are common findings in Fukuyama congenital muscular dystrophy (CMD) [28]. Neuropathological examinations revealed that cerebellar cysts in CMD are lined by leptomeningeal tissue. They are most likely formed from the subarachnoid spaces that were engulfed by the dysplastic cerebellar folia, particularly in the boundary between the normal and dysplastic cerebellar cortex [29]. Subsequently, similar imaging findings have been shown in muscle-eye-brain (MEB) disease [28]. Actually, the CMD spectrum covers a very broad and heterogeneous spectrum of disorders [30, 31].

Cerebellar cysts are rarely a feature of merosin-negative CMD [32, 33]. Cerebellar cysts, however, are mostly seen in many CMDs related to alpha-dystroglycans but are not equally prevalent in all forms [28]. Remarkably, they are not a

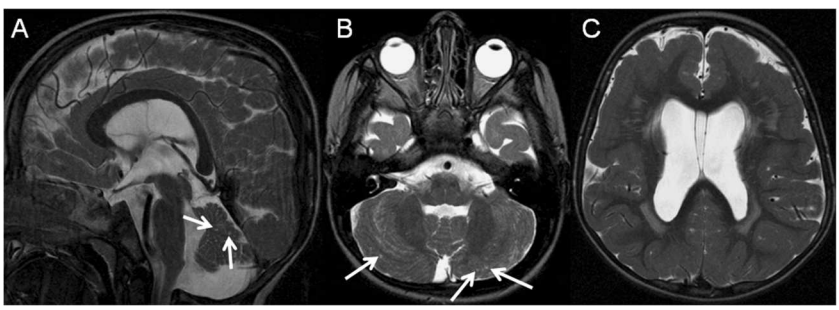

Fig. 3 A 3.5-year-old boy with *GPR56* mutation who has been investigated because of marked developmental delay and seizures. Midsagittal T2-weighted image (**a**) shows multiple cysts and dysplasia of the cerebellar vermis. Axial T2-weighted image (**b**) at the level of the posterior fossa reveals multiple small cysts in the posterior parts of the cerebellar hemispheres (*arrows*). Axial T2-weighted image (**c**) at the level of the lateral ventricles shows extensive, bilateral migration abnormality, hyperintense signal of the periventricular white matter, and mild ventriculomegaly

common feature of Walker-Warburg syndrome (WWS), for which actually 12 genes are associated [31]. Using constructive interference in steady state (CISS) sequence, Rathod et al. were able to demonstrate cerebellar cysts in a patient with WWS [34]. It is arguable that better imaging techniques will result in a higher yield of cerebellar cysts in CMD as well as in and other disorders. There is a clinical, imaging, and genetic overlap of some CMD forms [28]. Mutations in the following genes have been reported in association with cerebellar cysts: *FKTN* (Fukutin), *FKRP*, *POMGNT1*, *LARGE*, *ISPD*, *TMEM5*, *GMPPB*, *POMT1*, and *POMT2*.

Cirak et al. reported *ISPD* mutations in dystroglycanopathy phenotypes milder compared to WWS, namely ambulant patients with limb-girdle muscular dystrophy [35]. One child (patient 6) was found to have multiple cerebellar cysts. Remarkably, this boy had ocular motor apraxia and high myopia (as patients with *LAMA1* mutations, see below).

Another child with *B3GALNT2* mutations and a milder constellation than previously described is worth mentioning [36]. On neuroimaging, this ambulant girl had multiple subcortical cerebellar cysts, a hypoplastic pons, and supratentorial periventricular white matter signal abnormalities. It is rather the severity of the mutation than the affected gene that determines the severity of the clinical and imaging phenotype.

A very severe MEB-like phenotype was observed in Lybian siblings with a novel homozygous *DAG1* missense mutation. This is the first-reported beta-dystroglycan mutation with a human phenotype [37]. Infratentorial imaging findings included subcortical cerebellar cysts and pontine hypoplasia. Supratentorial abnormalities were very striking and consisting of diffusely swollen white matter with highly hyperintense T2 signal abnormality and multiple cysts. In addition, a migration disorder suggestive of polymicrogyria was noted.

Typical constellation: in the CMD spectrum, cerebellar cysts have a cortical-subcortical predilection in a "malformed" cerebellum with evidence of disturbed cortical architecture, often accompanied by alterations of the brain stem (hypoplastic pons, clefts), in various combinations with supratentorial abnormalities (white matter signal changes, polymicrogyria).

Cerebellar Cysts in *LAMA1* Mutations

Recently, we have drawn attention to a group of patients with ataxia, intellectually disability, and ocular motor apraxia, but no muscular weakness. Neuroimaging showed multiple cerebellar cysts, cerebellar dysplasia, abnormal shape of the fourth ventricle, normal brain stem morphology, and no supratentorial findings [38]. Cerebellar cysts were located mostly in the anterior and superior part of the vermis as well as in the posterior and superior regions of both cerebellar hemispheres. Figure 4 illustrates the characteristic imaging findings. We failed to identify the underlying genetic mutation. We speculated whether these patients may fall into the spectrum of alpha-dystroglycanopathies. Subsequently, we have identified additional patients matching this clinical and imaging pattern. Aldinger et al. (2014) have confirmed the clinical and MRI phenotype of our observation, reporting

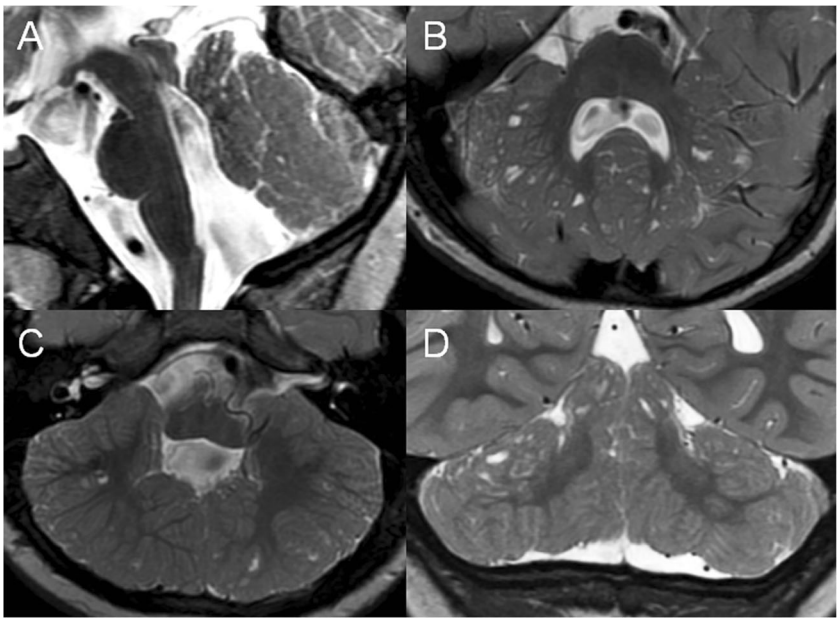

Fig. 4 Midsagittal (**a**), axial (**b**, **c**), and coronal (**d**) T2-weighted MR images of a 3.8-year-old child show multiple cortical/subcortical cysts located within the cerebellar vermis (anterior and superior part) and both cerebellar hemispheres (posterior and superior parts). Additional abnormalities illustrated the following: hypoplasia of the inferior part of the cerebellar vermis (**a**), bilateral cerebellar dysplasia (**b**–**d**), an enlarged fourth ventricle with a peculiar elongated and squared shape (**a**), an elongated midbrain (**a**), and a short pons (**a**). The imaging findings are suggestive of *LAMA1* mutation (reprinted with permission from Poretti A et al., *Cerebellum*, 2013)

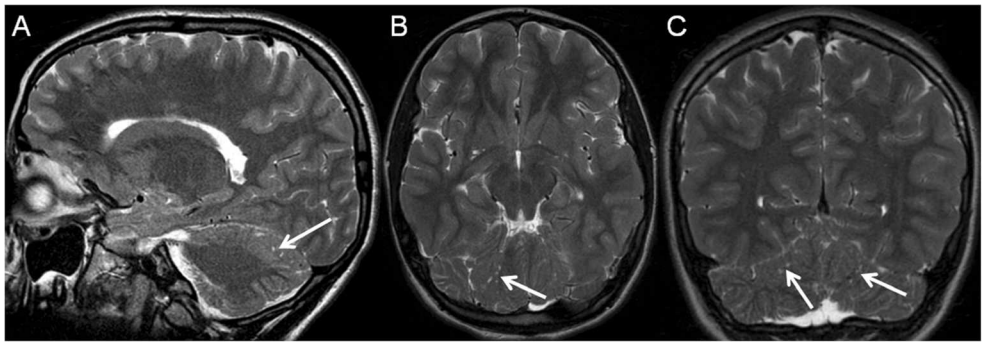

Fig. 5 A 11-year-old girl with non-progressive cerebellar ataxia, ocular motor apraxia, and normal cognitive functions. Midsagittal (**a**), axial (**b**), and coronal (**c**) T2-weighted images show multiple small cortical-subcortical cysts in the upper and posterior parts of the cerebellum (*arrows*). In addition, a diffuse cerebellar dysplasia is noted as disorganized cerebellar foliation, irregular white matter arborization, and irregular gray-white matter differentiation

seven patients from five families [39]. All patients had a history of delayed motor and speech milestones; 3/7 had ocular motor apraxia, and 5/7 high myopia. The clinical spectrum could be enlarged by observing retinal abnormalities in some patients. None of the patients had muscular involvement. The authors identified mutations in *LAMA1* mutations as the genotype of this clinical and imaging pattern. Remarkably, two mutation-positive siblings had cerebellar dysplasia and other imaging features described, but no cerebellar cysts. OMIM 615960 has been assigned to this entity (Poretti-Boltshauser syndrome).

Laminins are a large family of multidomain trimeric basement membrane proteins, which not only are important for the structure of extracellular matrix and adhesion, but also modulate cell behavior, influence differentiation, migration, and phenotypic stability [40]. The alpha-, beta-, and gamma-chains assemble to form a coiled coil in a least 16 combinations. Five isoforms of alpha-chains are known. Several laminopathies (as discussed in Aldinger et al.) are known resulting in involvement of the central and peripheral nervous systems as well as muscles; merosin-deficient CMD due to *LAMA2* mutation (affecting alpha-2 chain) is the best known example. However, cerebellar cysts were not recorded in these previously identified conditions [39].

Typical constellation: multiple cortical-subcortical cysts in the antero-superior vermis and posterior-superior aspects of the hemispheres, associated with dysplasia, vermis hypoplasia, abnormal configuration of the fourth ventricle, normal brain stem, and no supratentorial abnormalities.

Cerebellar Cysts in Cerebellar Dysplasia

The term cerebellar dysplasia refers to deranged development of the cerebellar tissue resulting in abnormal cerebellar foliation and fissuration. Abnormalities affect not only the cerebellar gray matter but also the architecture of the white matter as abnormal arborization and/or irregular cerebellar gray-white matter junction [41]. The term is not informative about the pathogenesis. The etiology is heterogeneous, both genetic and acquired causes are known. In the majority of cases, the exact pathogenesis remains unknown. The cysts are likely the result of disturbed cortical migration/organization and pial membrane disruption, explaining their cortical-subcortical location.

Neuroimaging in autosomal recessively inherited Chudley-McCullough syndrome (MIM 604213)

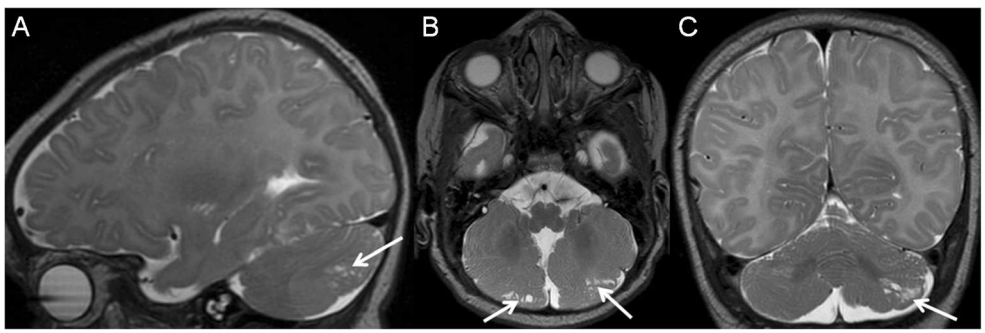

Fig. 6 A 4-month-old boy with hypotonia, bilateral ptosis, and unilateral congenital third nerve palsy. Midsagittal (**a**), axial (**b**), and coronal (**c**) T2-weighted images show multiple small cortical-subcortical cysts in the posterior and lateral aspects of the cerebellum (*arrows*). Additional anomalies (multiple periventricular heterotopias and olfactory bulb absence) are not illustrated

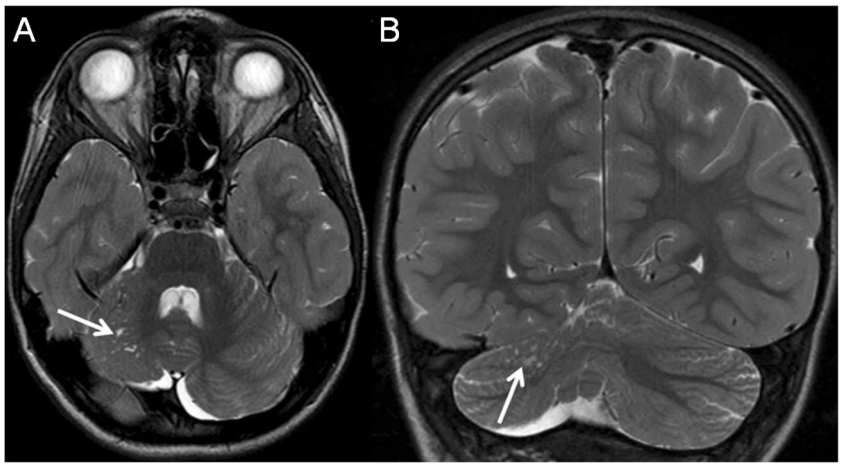

Fig. 7 A 6-year-old boy with the history of motor delay, moderate truncal ataxia, right predominant dysmetria, and normal cognition. Axial (**a**) and (**b**) coronal T2-weighted images show a markedly smaller and dysplastic right cerebellar hemisphere with multiple cysts (*arrows*)

demonstrates consistently bilateral cerebellar dysplasia, in addition to anomalies of the corpus callosum, hydrocephalus, and heterotopias; however, cerebellar cysts are not a feature [42, 43].

Cerebellar cysts were seen in siblings with mutation-positive (*VPS13B*) Cohen syndrome (MIM 216550). The literature about imaging in Cohen syndrome is scant, but apparently, most patients do not do have cerebellar cysts [44].

We have seen a few patients with *bilateral* cerebellar dysplasia with cerebellar cysts. It was not possible to reach a conclusive diagnosis beyond clinical and imaging description; therefore, the pathogenesis remains unknown. In these children, the indication for imaging was "cerebral palsy" or "developmental delay." Two representative patients are illustrated in Figs. 5 and 6.

We have also seen cerebellar cysts confined to *unilateral* cerebellar dysplasia in a hemisphere of reduced volume. In view of the "focal" nature of the anomalies, we tend to assume a prenatal acquired (i.e., disruptive) origin. So far, we have not seen cerebellar cysts in other cerebellar disruptive anomalies (as unilateral cerebellar hypoplasia, cerebellar clefts, or cerebellar disruption of prematurity) [45–48]. Two typical examples are shown in Figs. 7 and 8.

The literature on cysts in cerebellar dysplasia is very scant. Demaerel was one of few authors interested in the topic of cerebellar dysplasia [49–51]. However, he only mentioned two patients with "cyst-like changes" among four individuals with cerebellar cortical dysplasia, and one patient in a series of 42 individuals with abnormalities of cerebellar foliation and fissuration.

Typical constellation: cerebellar dysplasia is the dominant feature. Cysts are cortical-subcortical, confined to dysplastic areas, most likely located in the upper vermis and upper parts of the hemispheres, widespread or focal.

Miscellaneous

Leukoencephalopathy with Calcifications and Cysts

Livingston et al. reported the clinical and radiological features of a cohort of 15 patients with leukoencephalopathy with calcifications and cysts (LCC) [52]. They observed cerebellar cysts in two patients, but cysts were more prevalent in other locations (hemispheric white matter, basal ganglia/thalami, brain stem).

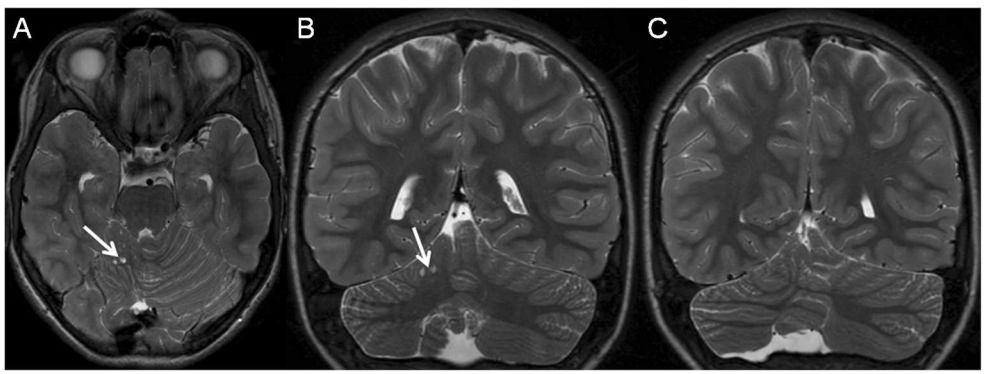

Fig. 8 A 11-year-old girl with the history of multiple hospital admissions for functional (non-organic) complaints, including headache. The neurological examination was normal. Axial (**a**) and coronal (**b**, **c**) T2-weighted images show a mild reduction in volume and dysplasia (irregular cerebellar foliation and white matter arborization) of the right cerebellar hemisphere and dysplasia. In addition, few cysts are noted in the upper and medial part of the right cerebellar hemisphere (*arrows* in **a**, **b**). These findings are considered "incidental"

Postcontrast enhancement is typically present around the cysts in areas with marked calcifications. All patients had displayed calcifications in multiple sites. Recognition of this disorder is not problematic in view of the overall pattern.

Early-Onset Multiple Carboxylase Deficiency (Holocarboxylase Synthetase Deficiency)

Multiple cerebellar cysts were found in fetal imaging in a patient with early-onset multiple carboxylase deficiency (OMIM 253270) [53]. We were unable to find additional reported cases with this metabolic disorder.

Conclusion

Consideration of the following aspects will assist in narrowing of the differential diagnosis and, if required, planning of targeted diagnostic workup:

1. *Cyst location*: cortical-subcortical, within the white matter, focal or widespread
2. *Cerebellar morphology*: cortical architecture, areas of dysplasia, hypoplasia, resulting in change in shape of the fourth ventricle
3. *Brain stem morphology*: hypoplastic pons, clefts, tectal dysplasia, and kinking
4. *Supratentorial abnormalities*: absence or presence of the following: migration anomalies, polymicrogyria, white matter signal abnormalities, cysts within the white matter, heterotopias, and hydrocephalus
5. *Clinical setting*: searching in particular for the following: muscle involvement, ataxia, ocular motor apraxia, intellectual disability, and ophthalmological abnormalities such as retinopathy, cataract, and high myopia

Acknowledgments We thank Asim F. Choudhri, MD, Department of Radiology, Le Bonheur Children's Hospital, Memphis, TN, USA, for sharing neuroimaging data of one patient.

Conflict of Interest All coauthors do not report conflicts of interest.

Funding This work was not supported by grants.

Author Contribution EB and AP conceptualized the article, and EB drafted the manuscript. All the coauthors critically revised the manuscript for intellectual content and read and approved the final manuscript.

References

1. Poretti A, Boltshauser E. Cerebellar cysts and neuroimaging in congenital muscular dystrophies. In: Boltshauser E, Schmahmann JD, editors. Cerebellar disorders in children. London: MacKeith Press; 2012. p. 177–83.
2. Barkovich AJ, Raybaud C. Pediatric neuroimaging. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2012.
3. Osborn AG. Osborn's brain: imaging, pathology, and anatomy. Philadelphia: Lippincott Williams & Wilkins; 2012.
4. Nickerson JP, Richner B, Santy K, et al. Neuroimaging of pediatric intracranial infection-part 2: TORCH, viral, fungal, and parasitic infections. J Neuroimaging. 2012;22:e52–63.
5. Poretti A, Meoded A, Huisman TA. Neuroimaging of pediatric posterior fossa tumors including review of the literature. J Magn Reson Imaging. 2012;35:32–47.
6. Reardon W, Donnai D. Dysmorphology demystified. Arch Dis Child Fetal Neonatal Ed. 2007;92:F225–9.
7. Hennekam RC, Biesecker LG, Allanson JE, et al. Elements of morphology: general terms for congenital anomalies. Am J Med Genet A. 2013;161A:2726–33.
8. Zafeiriou DI, Batzios SP. Brain and spinal MR imaging findings in mucopolysaccharidoses: a review. AJNR Am J Neuroradiol. 2013;34:5–13.
9. Alqahtani E, Huisman TA, Boltshauser E, et al. Mucopolysaccharidoses type I and II: new neuroimaging findings in the cerebellum. Eur J Paediatr Neurol. 2014;18:211–7.
10. Goh RH, Maguire J. Neuroepithelial cyst of the posterior fossa: two case reports with radiologic-pathologic correlation. Can Assoc Radiol J. 1996;47:126–31.
11. Marsh SE, Grattan-Smith P, Pereira J, Barkovich AJ, Gleeson JG. Neuroepithelial cysts in a patient with Joubert syndrome plus renal cysts. J Child Neurol. 2004;19:227–31.
12. Poretti A, Huisman TA, Scheer I, Boltshauser E. Joubert syndrome and related disorders: spectrum of neuroimaging findings in 75 patients. AJNR Am J Neuroradiol. 2011;32:1459–63.
13. Rudnik-Schoneborn S, Barth PG, Zerres K. Pontocerebellar hypoplasia. Am J Med Genet C: Semin Med Genet. 2014;166C: 173–83.
14. Barth PG. Pontocerebellar hypoplasias. An overview of a group of inherited neurodegenerative disorders with fetal onset. Brain Dev. 1993;15:411–22.
15. Barth PG, Aronica E, de Vries L, et al. Pontocerebellar hypoplasia type 2: a neuropathological update. Acta Neuropathol. 2007;114: 373–86.
16. Namavar Y, Barth PG, Kasher PR, et al. Clinical, neuroradiological and genetic findings in pontocerebellar hypoplasia. Brain. 2011;134: 143–56.
17. Eggens VR, Barth PG, Niermeijer JM, et al. EXOSC3 mutations in pontocerebellar hypoplasia type 1: novel mutations and genotype-phenotype correlations. Orphanet J Rare Dis. 2014;9:23.
18. Glamuzina E, Brown R, Hogarth K, et al. Further delineation of pontocerebellar hypoplasia type 6 due to mutations in the gene encoding mitochondrial arginyl-tRNA synthetase, RARS2. J Inherit Metab Dis. 2012;35:459–67.
19. Cassandrini D, Cilio MR, Bianchi M, et al. Pontocerebellar hypoplasia type 6 caused by mutations in RARS2: definition of the clinical spectrum and molecular findings in five patients. J Inherit Metab Dis. 2013;36:43–53.
20. Kastrissianakis K, Anand G, Quaghebeur G, et al. Subdural effusions and lack of early pontocerebellar hypoplasia in siblings with RARS2 mutations. Arch Dis Child. 2013;98:1004–7.
21. Hopkins B, Sutton VR, Lewis RA, Van den Veyver I, Clark G. Neuroimaging aspects of Aicardi syndrome. Am J Med Genet A. 2008;146A:2871–8.
22. Bahi-Buisson N, Poirier K, Boddaert N, et al. GPR56-related bilateral frontoparietal polymicrogyria: further evidence for an overlap with the cobblestone complex. Brain. 2010;133:3194–209.
23. Barkovich AJ. Current concepts of polymicrogyria. Neuroradiology. 2010;52:479–87.

24. Quattrocchi CC, Zanni G, Napolitano A, et al. Conventional magnetic resonance imaging and diffusion tensor imaging studies in children with novel GPR56 mutations: further delineation of a cobblestone-like phenotype. Neurogenetics. 2013;14:77–83.
25. Fujii Y, Ishikawa N, Kobayashi Y, Kobayashi M, Kato M. Compound heterozygosity in GPR56 with bilateral frontoparietal polymicrogyria. Brain Dev. 2013;36:528–31.
26. Luo R, Yang HM, Jin Z, et al. A novel GPR56 mutation causes bilateral frontoparietal polymicrogyria. Pediatr Neurol. 2011;45:49–53.
27. Li S, Jin Z, Koirala S, et al. GPR56 regulates pial basement membrane integrity and cortical lamination. J Neurosci. 2008;28:5817–26.
28. Clement E, Mercuri E, Godfrey C, et al. Brain involvement in muscular dystrophies with defective dystroglycan glycosylation. Ann Neurol. 2008;64:573–82.
29. Aida N, Yagishita A, Takada K, Katsumata Y. Cerebellar MR in Fukuyama congenital muscular dystrophy: polymicrogyria with cystic lesions. AJNR Am J Neuroradiol. 1994;15:1755–9.
30. Bonnemann CG, Wang CH, Quijano-Roy S, et al. Diagnostic approach to the congenital muscular dystrophies. Neuromuscul Disord. 2014;24:289–311.
31. Freeze HH, Chong JX, Bamshad MJ, Ng BG. Solving glycosylation disorders: fundamental approaches reveal complicated pathways. Am J Hum Genet. 2014;94:161–75.
32. Talim B, Ferreiro A, Cormand B, et al. Merosin-deficient congenital muscular dystrophy with mental retardation and cerebellar cysts unlinked to the LAMA2, FCMD and MEB loci. Neuromuscul Disord. 2000;10:548–52.
33. Triki C, Louhichi N, Meziou M, et al. Merosin-deficient congenital muscular dystrophy with mental retardation and cerebellar cysts, unlinked to the LAMA2, FCMD, MEB and CMD1B loci, in three Tunisian patients. Neuromuscul Disord. 2003;13:4–12.
34. Rathod SB, Baheti AD, Dabhade PT, Sankhe SS. Walker-Warburg syndrome: demonstration of cerebellar cysts with CISS sequence. Magn Reson Med Sci. 2012;11:137–40.
35. Cirak S, Foley AR, Herrmann R, et al. ISPD gene mutations are a common cause of congenital and limb-girdle muscular dystrophies. Brain. 2013;136:269–81.
36. Hedberg C, Oldfors A, Darin N. B3GALNT2 is a gene associated with congenital muscular dystrophy with brain malformations. Eur J Hum Genet. 2014;22:707–10.
37. Geis T, Marquard K, Rodl T, et al. Homozygous dystroglycan mutation associated with a novel muscle-eye-brain disease-like phenotype with multicystic leucodystrophy. Neurogenetics. 2013;14:205–13.
38. Poretti A, Häusler M, Von Moers A, et al. Ataxia, intellectual disability, and ocular apraxia with cerebellar cysts: a new disease? Cerebellum. 2014;13:79–88.
39. Aldinger KA, Mosca SJ, Tetreault M, et al. Mutations in LAMA1 cause cerebellar dysplasia and cysts with and without retinal dystrophy. Am J Hum Genet. 2014;95:227–34.
40. Domogatskaya A, Rodin S, Tryggvason K. Functional diversity of laminins. Annu Rev Cell Dev Biol. 2012;28:523–53.
41. Poretti A, Boltshauser E. Cerebellar dysplasia. In: Boltshauser E, Schmahmann JD, editors. Cerebellar disorders in children. London: MacKeith Press; 2012. p. 172–6.
42. Doherty D, Chudley AE, Coghlan G, et al. *GPSM2* mutations cause the brain malformations and hearing loss in Chudley-McCullough syndrome. Am J Hum Genet. 2012;90:1088–93.
43. Kau T, Veraguth D, Schiegl H, Scheer I, Boltshauser E. Chudley-McCullough syndrome: case report and review of the neuroimaging spectrum. Neuropediatrics. 2012;43:44–7.
44. Kivitie-Kallio S, Autti T, Salonen O, Norio R. MRI of the brain in the Cohen syndrome: a relatively large corpus callosum in patients with mental retardation and microcephaly. Neuropediatrics. 1998;29:298–301.
45. Poretti A, Leventer RJ, Cowan FM, et al. Cerebellar cleft: a form of prenatal cerebellar disruption. Neuropediatrics. 2008;39:106–12.
46. Poretti A, Huisman TA, Cowan FM, et al. Cerebellar cleft: confirmation of the neuroimaging pattern. Neuropediatrics. 2009;40:228–33.
47. Poretti A, Prayer D, Boltshauser E. Morphological spectrum of prenatal cerebellar disruptions. Eur J Paediatr Neurol. 2009;13:397–407.
48. Poretti A, Limperopoulos C, Roulet-Perez E, et al. Outcome of severe unilateral cerebellar hypoplasia. Dev Med Child Neurol. 2010;52:718–24.
49. Demaerel P, Lagae L, Casaer P, Baert AL. MR of cerebellar cortical dysplasia. AJNR Am J Neuroradiol. 1998;19:984–6.
50. Demaerel P, Wilms G, Marchal G. Rostral vermian cortical dysplasia: MRI. Neuroradiology. 1999;41:190–4.
51. Demaerel P. Abnormalities of cerebellar foliation and fissuration: classification, neurogenetics and clinicoradiological correlations. Neuroradiology. 2002;44:639–46.
52. Livingston JH, Mayer J, Jenkinson E, et al. Leukoencephalopathy with calcifications and cysts: a purely neurological disorder distinct from coats plus. Neuropediatrics. 2014;45:175–82.
53. Tsutsumi Y, Oka A, Itoh Y, et al. Cerebellar cysts associated with multiple carboxylase deficiency: a case report. Ultrasound Obstet Gynecol. 2010;35:634.